Approach to neonatal thrombocytopenia: immature platelet fraction has a major role

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Thrombocytopenia is extremely common in the neonatal intensive care unit (NICU) setting, occurring in upto a quarter of admissions^{1,2} but while the disorder is frequently seen it should not be dismissed without consideration of its significance.³ The evaluation and management of thrombocytopenia, which could be a marker of underlying disease as well as an obvious risk factor for haemorrhage is a frequent challenge for neonatologists.³ Neonatal thrombocytopenia is defined as a platelet count $<150 \times 10^9/L$ regardless of gestational age. However, platelet counts in the $100\text{--}150 \times 10^9/L$ range are somewhat more common among healthy neonates than among healthy adults.

Causes of neonatal thrombocytopenia are best separated by time of presentation into foetal (mainly TORCH infections), early (<3 days) and late.⁴ Though a large number of varied precipitating conditions have been identified, early-onset thrombocytopenia is most commonly associated with foeto-maternal conditions complicated by placental insufficiency and/or foetal hypoxia, e.g. maternal pre-eclampsia and foetal intrauterine growth restriction (IUGR).^{1,2} The thrombocytopenia is usually mild to moderate, resolves spontaneously and requires no specific therapy. Deviation from this pattern suggests the presence of more significant precipitating conditions. The most important of these are the immune thrombocytopenias and every NICU should develop investigation and treatment protocols to manage these cases promptly and avoid unnecessary risk of haemorrhage. In contrast, late-onset thrombocytopenia is almost always associated with sepsis or necrotizing enterocolitis (NEC) and the associated thrombocytopenia is severe, prolonged, often requiring treatment by platelet transfusion. Unfortunately, evidence-based guidelines for platelet transfusion therapy in NICU are currently unavailable leading to difficulty in defining accepted thresholds for transfusion thus leading to variations in transfusion practices.⁵

The article published in this issue, on the incidence of thrombocytopenia is a good step in identifying the magnitude of the problem in our setting.⁶ However, as the platelet count was determined as part of complete blood count (CBC) by the coulter cell counter if the authors had taken into account the

immature platelet fraction (IPF) which is a component of CBC, it would have helped know the likely cause as well as help predict the likely recovery.

Mean platelet volume (MPV) is an indicator of IPF and is similar to the reticulocyte count in the evaluation of anaemia. Mean platelet volume (MPV) is a measure of the average size of circulating platelets and can provide clues to the kinetic mechanism of an infant's thrombocytopenia. MPV is normal (7.5–9.5 fL) when thrombocytopenia is caused by reduced production, and elevated (10–12 fL) when caused by accelerated destruction. Larger platelets are evident when the bone marrow is stimulated to produce more immature platelets in response to increased platelet utilisation. Bone marrow biopsy is the gold standard for diagnosis of thrombocytopenia but is difficult and thus postponed till the infant is out of the neonatal period and in this situation the MPV is the best non-invasive alternative.⁴

The percentage of reticulated platelets (RPs) is another indicator of the kinetic mechanism. RPs are newly produced platelets having a higher ribonucleic acid content than do older platelets. RP% is low ($<2\%$) when platelet production is low, and high ($>10\%$) when platelets are being consumed at an accelerated rate. Thrombopoietin (Tpo), a growth factor, is the primary regulator of platelet production in the neonate. Plasma Tpo may be useful in differentiating thrombocytopenia caused by low platelet production and accelerated platelet destruction. Synthesised in the liver, Tpo is removed from the blood by binding to Tpo receptors on megakaryocyte progenitors, megakaryocytes, and platelets. When platelet production is low or fewer megakaryocytes are produced, the plasma Tpo is high. Although still a research tool, measurement of plasma Tpo may provide valuable diagnostic information in infants with thrombocytopenia in the future.^{1,7,8}

The nuances have been illustrated with two cases in NICU.

Case 1: A 38 weeks' gestation neonate with platelet count $<50 \times 10^9/L$ since birth. At five days of age: stools are occult blood positive; platelet count is $15 \times 10^9/L$; MPV is 7.3 fL. Thus, the underlying cause of low platelets is reduced platelet production. Transfused platelets will have a normal survival.

Case 2: A contrasting situation is a 29 weeks' gestation appropriate for gestational age neonate who had normal platelet count at birth. At 25 days of age, recovering from NEC, while on parenteral nutrition and antibiotics: platelet count has been $30\text{--}40 \times 10^9/L$ for one week; mean platelet volume 12 fL. The underlying cause in this situation is accelerated platelet usage or destruction. Platelets transfused into this infant are likely to have a short survival.

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APPROACH TO MANAGEMENT OF NEONATE WITH THROMBOCYTOPENIA

Most cases of neonatal thrombocytopenia are mild to moderate and do not warrant intervention. However, if the platelets count is $<50 \times 10^9/L$, the therapy with platelet transfusions is considered to decrease the risk of haemorrhage. The existing evidence to establish platelet transfusion triggers in neonates is very limited, but it suggests that transfusing platelets to non-bleeding neonates with platelet counts $<50 \times 10^9/L$ does not decrease the risk of intraventricular haemorrhage (IVH), and that $30 \times 10^9/L$ might be an adequate threshold for stable non-bleeding neonates.^{8,9} Thus what is required is careful follow-up and expectant management in an otherwise healthy appearing neonate with transient thrombocytopenia in this mild range is acceptable, and any worsening of thrombocytopenia or changes in clinical condition should prompt further evaluation.

Increased platelet consumption underlies the thrombocytopenia of sepsis or necrotizing enterocolitis (NEC), while decreased platelet production is thought to underlie the thrombocytopenia seen in neonates born to mothers with severe placental insufficiency. However, in any neonate with early or late onset thrombocytopenia, infection has to be considered at the top of the differential diagnosis, because a delay in this diagnosis can have life-threatening consequences. A mild to moderate thrombocytopenia, present at or shortly after birth in a well-appearing preterm infant without risk factors for infection and with a history of maternal pre-eclampsia or IUGR is most likely benign and the platelet count normalises within two weeks. Platelet counts $<50 \times 10^9/L$ or thrombocytopenia in a clinically ill neonate, in contrast, are unlikely to be secondary to placental insufficiency, and other diagnoses such as sepsis and neonatal alloimmune thrombocytopenia (NAIT) should be considered.^{1,2,10}

In patients with early-onset thrombocytopenia on whom sepsis and NAIT has been excluded a detailed family history and physical exam can provide critical clues to the diagnosis. It is particularly important to know the maternal platelet count to rule out autoimmune thrombocytopenia. The affected neonate should be carefully evaluated for any radial abnormalities (suggestive of thrombocytopenia-absent radii syndrome or Fanconi anaemia) and any inability to rotate the forearm (as in the rare congenital amegakaryocytic thrombocytopenia with proximal radio-ulnar synostosis).¹¹ The presence of hepato or splenomegaly is also important to establish the differential diagnosis as accompanying pancytopenia suggests a diagnosis of osteopetrosis.

In the absence of any obvious diagnostic clues in the history and physical exam, the most common cause of isolated severe thrombocytopenia in an otherwise well-appearing infant is NAIT, caused by the passage of antiplatelet antibodies from the mother to the foetus. If the NAIT work-up is negative, then a more detailed evaluation is indicated, including testing for viral infections and chromosome analysis to exclude disorders that sometimes present only with thrombocytopenia accompanied by unexplained IUGR and/or very subtle dysmorphic features (i.e. 11q terminal deletion or Jacobsen syndrome).¹⁰⁻¹² Rarer diagnoses, such as Kasabach-Merritt syndrome, inborn

errors of metabolism (mainly propionic academia and methylmalonic academia) or renal vein thrombosis should be considered and evaluated when clinically indicated.¹⁰

When a neonate develops thrombocytopenia of any severity at greater than 72 hours of life, the most likely cause is bacterial or fungal sepsis and/or NEC. If infection and NEC are excluded as aetiologies for the thrombocytopenia, then the evaluation should be expanded. This should include testing for: liver dysfunction, DIC, viral infections like HSV or acquired CMV, thrombosis in venous lines, and drug-induced thrombocytopenia. Immune thrombocytopenias should also be considered, because they generally worsen in the first few days of life and sometimes present after 72 hours of life.¹²

Significant variation is observed in NICU platelet transfusion practice as recently reported in the United States and Canada by Josephson et al.¹³ They reported that platelet transfusions are commonly given to non-bleeding neonates whose platelet counts fall below arbitrary limits. Such limits are based on "level IV" evidence, meaning not based on studies but on the recommendations of respected authorities. The benefits of platelet transfusions to non-bleeding neonates are speculative. Moreover, providing platelet transfusions to non-bleeding neonates with platelet counts of $<10-20 \times 10^9/L$ is not in keeping with current transfusion practice in adults. A recent study found no relationship between the lowest platelet count recorded and the mortality rate. However, a direct relationship was observed between the number of platelet transfusions received and the mortality rate.⁷ A similar relationship was identified and evaluated in a previous study that involved 1600 neonates with thrombocytopenia.⁸

Multi-centric studies are required to provide evidence based guidelines for transfusion practices in the NICU. Additionally evaluation of the immature platelet fraction should form a part of the work up for thrombocytopenia in NICU as they would provide information on the cause as well as the frequency of blood transfusion required based on a simple index like MPV.

REFERENCES

1. Sola-Visner M, Sallmon H, Brown R. New insights into the mechanisms of nonimmune thrombocytopenia in neonates. *Semin Perinatol* 2009;33:43-51.
2. Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the neonate. *Blood Rev* 2008;22:173-186.
3. Bussel JB, Sola-Visner M. Current approaches to the evaluation and management of the fetus and neonate with immune thrombocytopenia. *Semin Perinatol* 2009;33:35-42.
4. Sola MC. Evaluation and treatment of severe and prolonged thrombocytopenia in neonates. *Clin Perinatol* 2004;31:1-14.
5. Baer VL, Lambert DK, Schmutz N, et al. Adherence to NICU transfusion guidelines: data from a multihospital healthcare system. *J Perinatol* 2008;28:492-497.
6. Gupta A, Mathai S, Kanitkar M. Incidence of thrombocytopenia in the neonatal intensive care unit. *MJAFI* 2011;67:234-236.
7. Baer VL, Lambert DK, Henry E. Severe Thrombocytopenia in the NICU. *Pediatrics* 2009;124:1095-1100.

8. Baer VL, Lambert DK, Henry E, Snow GL, Sola-Visner MC, Christensen RD. Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopenic neonates in a multihospital healthcare system. *J Perinatol* 2007;27:790–796.
9. Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. *J Perinatol* 2009;29:130–133.
10. McPherson RJ, Juul S. Patterns of thrombocytosis and thrombocytopenia in hospitalized neonates. *J Perinatol* 2005;25:166–172.
11. Rivers A, Slayton WB. Congenital cytopenias and bone marrow failure syndromes. *Semin Perinatol* 2009;33:20–28.
12. Rodgers GM, Lehman CM. Diagnostic approach to the bleeding disorders. In: *Wintrobe's Clinical Hematology*, Greer JP, Forester J, Rodgers GM, et al, eds. Philadelphia, PA: Lippincott Williams and Wilkins 2009:1273–1275.
13. Josephson CD, Su LL, Christensen RD, et al. Platelet transfusion practices among neonatologists in the United States and Canada: results of a survey. *Pediatrics* 2009;123:278–285.